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(57) Abstract

A class of substituted 1,2,4–triazolo[4,3–*b*]pyridazine derivatives, possessing an optionally substituted phenyl ring at the 3–position, and a C–substituted triazolyl–methoxy moiety at the 6–position, are selective ligands for $GABA_A$ receptors, in particular having high affinity for the $\alpha 2$ and/or $\alpha 3$ subunit thereof, and are accordingly of benefit in the treatment and/or prevention of disorders of the central nervous system, including anxiety and convulsions.

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TRIAZOLO-PYRIDAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

The present invention relates to a class of substituted triazolo-pyridazine derivatives and to their use in therapy. More particularly, this invention is concerned with substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious mental states.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha2$ and/or $\alpha3$ subunit than with $\alpha1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha1$ might be employed to reverse sedation or hypnosis caused by $\alpha1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; and hearing loss. Selective ligands for $GABA_A$ receptors may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

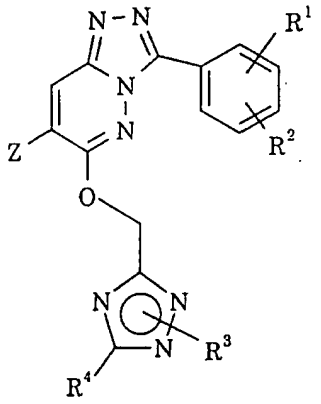
WO 98/04559 describes a class of substituted and 7,8-ring fused 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are stated to be selective ligands for $GABA_A$ receptors beneficial in the treatment and/or prevention of neurological disorders including anxiety and convulsions.

The present invention provides a class of triazolo-pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the $\alpha 2$ and/or $\alpha 3$ subunit of the human $GABA_A$ receptor. The compounds of this invention may interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with the $\alpha 1$ subunit. Desirably, the compounds of the invention will exhibit functional selectivity in terms of a selective efficacy for the $\alpha 2$ and/or $\alpha 3$ subunit relative to the $\alpha 1$ subunit.

The compounds of the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the $\alpha 2$ and/or $\alpha 3$ subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the $\alpha 2$ and/or $\alpha 3$ subunit relative to the $\alpha 1$ subunit. However, compounds which are not selective in terms of their binding affinity for the $\alpha 2$ and/or $\alpha 3$ subunit relative to the $\alpha 1$ subunit are also encompassed within the

scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit. Moreover, the compounds according to the present invention may possess interesting pharmacokinetic properties, notably in terms of improved oral bioavailability.

The present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein

Z represents *tert*-butyl, cyclobutyl, phenyl or pyrrolidin-1-yl;

R^1 represents hydrogen, methyl, methoxy or fluoro;

R^2 represents hydrogen or fluoro;

R^3 represents hydrogen, methyl or ethyl;

R^4 represents trifluoromethyl, chloromethyl, or a group of formula $-CH_2OR^a$ or $-CH_2NR^bR^c$;

R^a represents hydrogen, methyl or *tert*-butyldimethylsilanyl; and

R^b and R^c both represent methyl; or R^b and R^c together represent the residue of an azetidine, 3,3-difluoroazetidine, pyrrolidine, morpholine or *N*-methylpiperazine moiety.

Certain compounds in accordance with the present invention are encompassed within the generic scope of WO 98/04559. There is, however,

no specific disclosure therein of compounds corresponding to those of formula I as defined above.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of formula I include acid addition salts which may, for example, be formed by mixing a solution of the compound of formula I with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

In the compounds of formula I above, the moiety Z suitably represents *tert*-butyl, phenyl or pyrrolidin-1-yl.

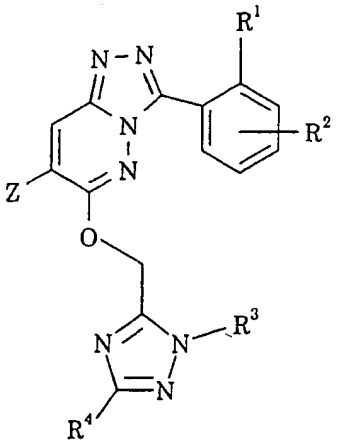
Suitably, R^1 represents hydrogen or fluoro.

Suitably, R^2 represents hydrogen.

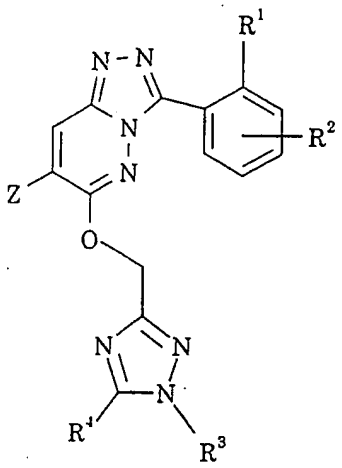
Suitably, R^3 represents methyl or ethyl.

Suitably, R^a represents hydrogen or methyl.

Particular sub-classes of compounds according to the invention are represented by the compounds of formula IIA and IIB, and pharmaceutically acceptable salts thereof:



(IIA)



(IIB)

wherein Z, R^1, R^2, R^3 and R^4 are as defined above.

Specific compounds within the scope of the present invention include:

N-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol;

N-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

[1-methyl-5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1*H*-1,2,4-triazol-3-yl]methanol;

6-(5-chloromethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

N-[5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

6-[2-methyl-5-(morpholin-4-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[5-(azetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[2-methyl-5-(4-methylpiperazin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[5-(3,3-difluoroazetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[2-methyl-5-(pyrrolidin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;

[5-(7-*tert*-butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(5-methoxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(2-methyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-methyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(2-ethyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-ethyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

and pharmaceutically acceptable salts thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient

in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of the compounds of the invention is ideally 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

The compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk- fibroblast cells.

The compounds according to the present invention exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds of the invention are substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, **10**, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block

pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

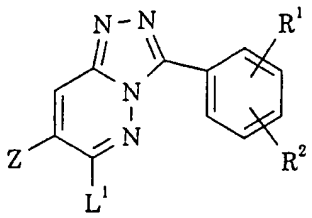
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets

or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

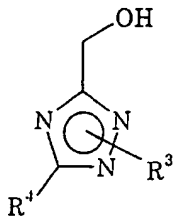
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of anxiety, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



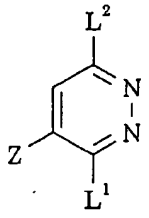
(IV)

wherein Z, R^1, R^2, R^3 and R^4 are as defined above, and L^1 represents a suitable leaving group.

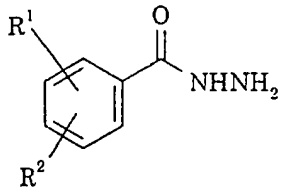
The leaving group L^1 is typically a halogen atom, especially chloro.

The reaction between compounds III and IV is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride.

The intermediates of formula III above may be prepared by reacting a compound of formula V with a substantially equimolar amount of a hydrazine derivative of formula VI:



(V)



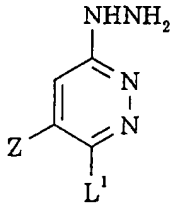
(VI)

wherein Z, R^1, R^2 and L^1 are as defined above, and L^2 represents a suitable leaving group; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

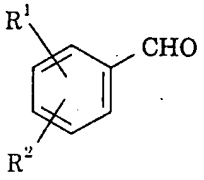
The leaving group L^2 is typically a halogen atom, especially chloro. In the intermediates of formula V, the leaving groups L^1 and L^2 may be the same or different, but are suitably the same, preferably both chloro.

The reaction between compounds V and VI is conveniently effected by heating the reactants in the presence of a proton source such as triethylamine hydrochloride, typically at reflux in an inert solvent such as xylene or 1,4-dioxane.

Alternatively, the intermediates of formula III above may be prepared by reacting a hydrazine derivative of formula VII with an aldehyde derivative of formula VIII:



(VII)



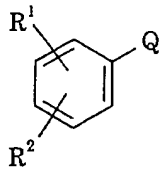
(VIII)

wherein Z, R^1, R^2 and L^1 are as defined above; followed by cyclization of the intermediate Schiff's base thereby obtained.

The reaction between compounds VII and VIII is conveniently effected under acidic conditions, for example in the presence of a mineral acid such as hydrochloric acid. Cyclization of the resulting Schiff's base intermediate may then conveniently be carried out by treatment with lead(IV) acetate in acetic acid or with iron(III) chloride in a suitable solvent, e.g. an alcoholic solvent such as ethanol, at an elevated temperature, typically at a temperature in the region of 60-70°C.

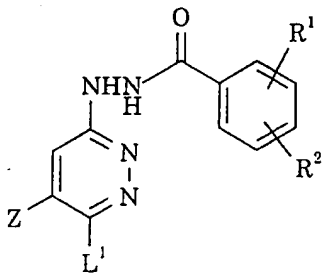
The intermediates of formula VII above may be prepared by reacting the appropriate compound of formula V as defined above with hydrazine hydrate, typically in 1,4-dioxane at the reflux temperature of the solvent; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

In an alternative approach, the intermediates of formula III above may be prepared by reacting the hydrazine derivative of formula VII as defined above with a compound of formula IX:



(IX)

wherein R^1 and R^2 are as defined above, and Q represents a reactive carboxylate moiety; followed by cyclization of the hydrazide derivative of formula X thereby obtained:



(X)

wherein Z, R^1, R^2 and L^1 are as defined above.

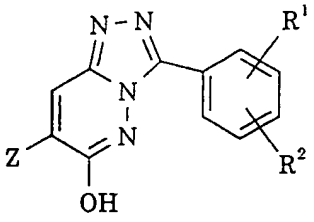
Suitable values for the reactive carboxylate moiety Q include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles. Suitably, Q represents an acid chloride moiety.

The reaction between compounds VII and IX is conveniently effected under basic conditions, e.g. in the presence of triethylamine, suitably in an inert solvent such as diethyl ether, and typically at a temperature in the

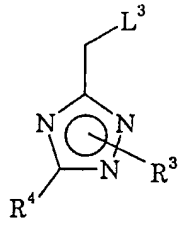
region of 0°C. Cyclization of the resulting compound of formula X may then conveniently be carried out by treatment with 1,2-dibromo-1,1,2,2-tetrachloroethane and triphenylphosphine, in the presence of a base such as triethylamine, suitably in an inert solvent such as acetonitrile, and typically at a temperature in the region of 0°C.

The reaction between compound V and hydrazine hydrate or compound VI will, as indicated above, usually give rise to a mixture of isomeric products depending upon whether the hydrazine nitrogen atom displaces the leaving group L^1 or L^2. Thus, in addition to the required product of formula III, the isomeric compound wherein the moiety Z is attached at the 8-position will usually be obtained to some extent; and likewise for compound VII. For this reason it will generally be necessary to separate the resulting mixture of isomers by conventional methods such as chromatography.

In another procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XI (or its 1,2,4-triazolo[4,3-*b*]pyridazin-6-one tautomer) with a compound of formula XII:



(XI)



(XII)

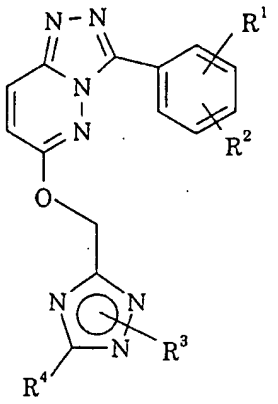
wherein Z, R^1, R^2, R^3 and R^4 are as defined above, and L^3 represents a suitable leaving group.

The leaving group L^3 is suitably a halogen atom, typically chloro or bromo.

The reaction between compounds XI and XII is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride.

The intermediates of formula XI above may conveniently be prepared by reacting a compound of formula III as defined above with an alkali metal hydroxide, e.g. sodium hydroxide. The reaction is conveniently effected in an inert solvent such as aqueous 1,4-dioxane, ideally at the reflux temperature of the solvent.

In a further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula Z-CO_2H with a compound of formula XIII:



(XIII)

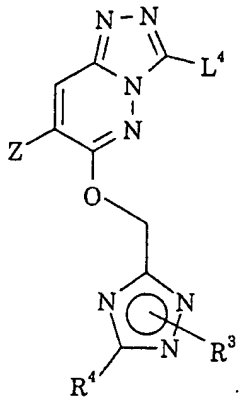
wherein Z, R^1, R^2, R^3 and R^4 are as defined above; in the presence of silver nitrate and ammonium persulphate.

The reaction is conveniently carried out in a suitable solvent, for example water or aqueous acetonitrile, optionally under acidic conditions, e.g. using sulphuric acid, typically at an elevated temperature.

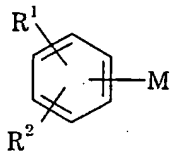
The intermediates of formula XIII correspond to the compounds of formula I as defined above wherein Z is hydrogen, and they may therefore

be prepared by methods analogous to those described above for preparing the corresponding compounds of formula I.

In a still further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

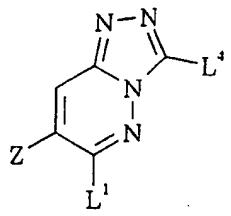
wherein Z, R^1, R^2, R^3 and R^4 are as defined above, M represents $-B(OH)_2$ or $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, typically *n*-butyl, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

The leaving group L^4 is suitably a halogen atom, e.g. bromo.

A suitable transition metal catalyst of use in the reaction between compounds XIV and XV comprises dichlorobis(triphenylphosphine)-palladium(II) or tetrakis(triphenylphosphine)palladium(0).

The reaction between compounds XIV and XV is conveniently effected in an inert solvent such as *N,N*-dimethylformamide, typically at an elevated temperature.

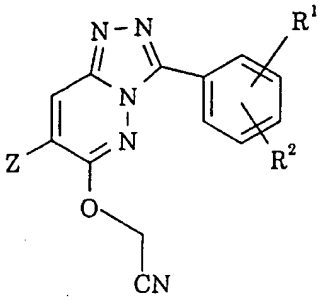
The intermediates of formula XIV may be prepared by reacting a compound of formula IV as defined above with a compound of formula XVI:



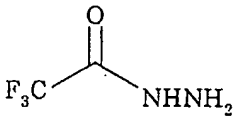
(XVI)

wherein Z, L^1 and L^4 are as defined above; under conditions analogous to those described above for the reaction between compounds III and IV.

In a yet further procedure, the compounds of formula I wherein R^4 represents trifluoromethyl and R^3 is hydrogen may be prepared by a process which comprises reacting a compound of formula XVII with the hydrazide of formula XVIII:



(XVII)



(XVIII)

wherein Z, R^1 and R^2 are as defined above.

The reaction is conveniently accomplished by treating compound XVII with sodium methoxide in methanol, neutralising with acetic acid, adding hydrazide XVIII and heating in a solvent such as methanol at a temperature typically in the region of 60°C.

The intermediates of formula XVII above may be prepared by reacting the appropriate compound of formula XI (or its 1,2,4-triazolo[4,3-*b*]pyridazin-6-one tautomer) as defined above with a compound of formula

L^3-CH_2CN, wherein L^3 is as defined above, under conditions analogous to those described above for the reaction between compounds XI and XII.

The hydrazide of formula XVIII above may be prepared as described in *Magn. Reson. Chem.*, 1990, 28, 331-336.

Where they are not commercially available, the starting materials of formula IV, V, VI, VIII, IX, XII, XV and XVI may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I initially obtained wherein R^3 is hydrogen may be converted into a corresponding compound wherein R^3 represents methyl or ethyl by standard alkylation procedures, typically by treatment with iodomethane or iodoethane in the presence of sodium hydride and *N,N*-dimethylformamide. A compound of formula I initially obtained wherein R^4 represents a group of formula $-CH_2OR^a$ and R^a represents *tert*-butyldimethylsilanyl may be converted into the corresponding compound wherein R^a is hydrogen using conventional protodesilylation procedures, typically by heating in ethanolic hydrochloric acid. The resulting compound of formula I wherein R^4 represents $-CH_2OH$ may be converted into the corresponding compound wherein R^4 represents $-CH_2OR^a$ and R^a is methyl by methylating with iodomethane in the presence of sodium hydride and *N,N*-dimethylformamide. Alternatively, a compound of formula I wherein R^4 represents $-CH_2OH$ may be converted into the corresponding compound wherein R^4 represents chloromethyl by stirring in phosphorus oxychloride. In addition, a compound of formula I wherein R^4 represents $-CH_2OH$ may be converted into the corresponding compound wherein R^4 represents $-CH_2NR^bR^c$ in a two-step process which comprises oxidising the $-CH_2OH$ moiety to -CHO by treatment with oxalyl

chloride and dimethylsulphoxide in the presence of triethylamine and dichloromethane; followed by treatment of the resulting aldehyde derivative with the appropriate amine of formula H-NR^bR^c in the presence of a reducing agent such as sodium cyanoborohydride. A compound of formula I wherein R^4 represents chloromethyl may be converted into a corresponding compound wherein R^4 represents -$CH_2NR^bR^c$ by treatment with the appropriate amine of formula H-NR^bR^c, typically with heating in the presence of sodium hydride and *N,N*-dimethylacetamide.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the α2 or α3 subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for α1β3γ2 cells; 18 nM for α2β3γ2 cells; 10 nM for α3β3γ2 cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of

[^{3}H]-flumazenil from the α2 and/or α3 subunit of the human $GABA_A$ receptor of 100 nM or less.

EXAMPLE 1

N-[5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine

a) 4-Phenyl-1,2-dihydropyridazine-3,6-dione

Phenylmaleic anhydride (30 g, 0.17 mol), sodium acetate trihydrate (28 g, 0.21 mol) and hydrazine monohydrate (10 ml, 0.21 mol) were heated together at reflux in 40% acetic acid (600 ml) for 18 h. The mixture was cooled at 7°C for 2 h, then filtered. The solid was washed with diethyl ether and dried *in vacuo* to give 11 g (34%) of the title compound: ^{1}H NMR (250 MHz, DMSO-*d*$_6$) δ 7.16 (1H, br s), 7.44 (5H, m), 7.80 (2H, br s); MS (ES^+) m/e 189 [MH^+].

b) 3,6-Dichloro-4-phenylpyridazine

4-Phenyl-1,2-dihydropyridazine-3,6-dione (3.4 g, 18 mmol) was heated at reflux in phosphorus oxychloride (70 ml) for 6 h. The solution was concentrated *in vacuo*, then the residue was dissolved in dichloromethane (100 ml) and was neutralised by the addition of cold 10% aqueous sodium hydrogen carbonate (150 ml). The aqueous phase was washed with dichloromethane (2 x 50 ml), then the combined organic layers were washed with saturated aqueous sodium chloride (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to yield 3.9 g (97%) of the title compound: ^{1}H NMR (250 MHz, DMSO-*d*$_6$) δ 7.54-7.66 (5H, m), 8.14 (1H, s); MS (ES^+) m/e 225/227/229 [MH^+].

c) 6-Chloro-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine

3,6-Dichloro-4-phenylpyridazine (2.9 g, 13 mmol), benzoic hydrazide (1.9 g, 21 mmol) and triethylammonium chloride (2.0 g, 14 mmol) were heated together at reflux in xylene (150 ml) for three days. More benzoic hydrazide (0.88 g, 6.5 mmol) was added and the mixture was heated as before for another day. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (silica gel, 0-50% EtOAc/CH_2Cl_2) to afford 1.4 g (36%) of the title compound as a solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55 (8H, m), 8.12 (1H, s), 8.50 (2H, m); MS (ES^+) m/e 307/309 [MH^+].

d) 5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazole-3-carbaldehyde

To 3-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-1*H*-1,2,4-triazole (EP-A-0421210) (0.50 g, 2.2 mmol) in THF (10 ml) was added butyllithium (1.5 ml of a 1.6 M solution in hexanes, 2.3 mmol) dropwise at -40°C with stirring. The solution was stirred at -40°C under nitrogen for 15 min, then DMF (0.18 ml, 0.17 g, 2.3 mmol) was added, and the mixture was allowed to warm to room temperature over 90 min. Saturated aqueous ammonium chloride (5 ml) was added, then the organic phase was separated, diluted with ethyl acetate (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 50% EtOAc/hexane) to give 0.29 g (56%) of the title compound as a colourless solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.14 (6H, s), 0.93 (9H, s), 4.18 (3H, s), 4.80 (2H, s), 9.98 (1H, s); MS (ES^+) m/e 288 [M + MeOH]$^+$.

e) *N*-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine

To 5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazole-3-carbaldehyde (0.23 g, 0.88 mmol) in methanol (15 ml) were added 3 Å molecular sieves (180 mg) and dimethylamine (0.49 ml of a 2 M

solution in methanol, 0.98 mmol) at room temperature with stirring. The mixture was stirred at room temperature under nitrogen for 1 h. Sodium cyanoborohydride (63 mg, 1.0 mmol) was added and the resultant mixture was stirred at room temperature under nitrogen for 3 h, with the pH of the solution being maintained at 5 by the addition of methanolic hydrogen chloride as necessary (methyl orange indicator). The solution was diluted with water (70 ml) and saturated aqueous sodium hydrogen carbonate was added until the pH was approximately 8. The solution was then washed with dichloromethane (3 x 50 ml). The organic layers were combined, washed with saturated aqueous sodium chloride (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 0-5% $MeOH/CH_2Cl_2$) to afford 0.20 g (81%) of the title compound as a solid: ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.92 (9H, s), 2.26 (6H, s), 3.57 (2H, s), 3.90 (3H, s), 4.75 (2H, s); MS (ES^+) m/e 285 [MH^+].

f) *N*-(5-Hydroxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-*N*,*N*-dimethylamine

To *N*-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine (0.19 g, 0.69 mmol) in ethanol (3 ml) was added 4 N sodium hydroxide solution (0.34 ml), and the solution was stirred at 45°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 10% $MeOH/CH_2Cl_2$) to yield 71 mg (61%) of the title compound as a colourless solid: ^1H NMR (360 MHz, $CDCl_3$) δ 2.26 (6H, s), 3.57 (2H, s), 3.90 (3H, s), 4.68 (2H, s); MS (ES^+) m/e 171 [MH^+].

g) *N*-[5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine hydrochloride

To *N*-(5-hydroxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-*N*,*N*-dimethylamine (71 mg, 0.42 mmol) in DMF (5 ml) was added sodium

hydride (33 mg of a 60% dispersion in mineral oil, 0.83 mmol), and the resultant slurry was stirred at room temperature under nitrogen for 5 min. 6-Chloro-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine (from step c) (0.11 g, 0.35 mmol) was added and the mixture was stirred as before for 5 min. Water (50 ml) was added and the resultant precipitate was filtered off, and was then purified by flash chromatography (silica gel, 0-5% $MeOH/CH_2Cl_2$). The product was taken up in methanolic hydrogen chloride (2 ml), concentrated *in vacuo*, and recrystallised from ethanol/diethyl ether, to give 9.0 mg (5%) of the title compound as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 2.81 (6H, s), 3.92 (3H, s), 4.53 (2H, s), 5.59 (2H, s), 7.50 (2H, m), 7.58 (1H, m), 7.64 (3H, m), 7.75 (2H), 8.44 (1H, s), 8.49 (2H, m), 10.52 (1H, br s); MS (ES^+) m/e 441 [MH^+].

EXAMPLE 2

[5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol

a) [5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-yl]methanol

To 3-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-1*H*-1,2,4-triazole (EP-A-0421210) (3.5 g, 0.015 mol) in THF (70 ml) was added *n*-butyllithium (10.2 ml of 1.6 M solution in hexanes, 0.016 mol) dropwise with stirring at -40°C. The solution was stirred at -40°C under nitrogen for 15 min, then DMF (1.3 ml, 1.2 g, 0.016 mol) was added and the mixture was allowed to warm to room temperature over 90 min. Methanol (20 ml) was added, and the solution was cooled to 0°C. Sodium borohydride (0.64 g, 0.017 mol) was added and the slurry was stirred for 5 min, during which time it cleared to a solution. Saturated aqueous sodium chloride (50 ml) was added, then the mixture was filtered to remove insoluble material. The organic phase of the filtrate was dried ($MgSO_4$), and concentrated *in*

vacuo. The residue was taken up in dichloromethane (50 ml), filtered to remove insoluble material, and the filtrate was concentrated *in vacuo* to yield 3.3 g (83%) of the title compound as a colourless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 3.89 (3H, s), 4.68 (2H, s), 4.72 (1H, br s); MS (ES^+) m/e 258 [MH^+].

b) 6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 72% yield using the procedure described in Example 1, step g, with [5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-yl]methanol being used instead of *N*-(5-hydroxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-*N*,*N*-dimethylamine. Data for the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 3.70 (3H, s), 4.73 (2H, s), 5.64 (2H, s), 7.46-7.59 (8H, m), 8.06 (1H, s), 8.44 (2H, m); MS (ES^+) m/e 528 [MH^+].

c) [5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol

6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine (0.58 g, 1.1 mmol) was stirred in a mixture of ethanol (10 ml) and 2 N hydrochloric acid (20 ml) at 60°C for 1 h. The solution was allowed to cool to room temperature, and the pH was adjusted to >7 with saturated sodium hydrogen carbonate solution, precipitating the title compound as a colourless solid (0.41 g, 90%). The material was recrystallised to analytical purity from ethanol. Data for the title compound: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.49 (1H, t, *J* 5.8 Hz), 3.71 (3H, s), 4.73 (2H, d, *J* 5.8 Hz), 5.64 (2H, s), 7.47-7.60 (8H, m), 8.06 (1H, s), 8.43 (2H, m); MS (ES^+) m/e 414 [MH^+].

EXAMPLE 3

N-[5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine

To oxalyl chloride (63 µl, 92 mg, 0.73 mmol) in dichloromethane (15 ml) was added DMSO (110 µl, 1.5 mmol) with stirring at -78°C, and the resultant solution was stirred at -78°C under nitrogen for 30 min. [5-(3,7-Diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol (from Example 2, step c) (0.25 g, 0.61 mmol) was added, and the mixture was stirred as before for 90 min. Triethylamine (0.42 ml, 0.31 g, 3.0 mmol) was added and the solution was stirred at -78°C under nitrogen for 15 min, then allowed to warm to room temperature over 90 min. Water was added with vigorous stirring, then the aqueous phase was washed with dichloromethane (2 x 15 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in methanol (10 ml), then 3 Å molecular sieves (0.20 g) and dimethylamine (0.33 ml of a 2 M solution in methanol, 0.67 mmol) were added. The slurry was stirred at room temperature for 30 min under nitrogen, then sodium cyanoborohydride (58 mg, 0.93 mmol) was added. The slurry was stirred as before for 24 h, maintaining the pH of the solution at 5 by the addition of methanolic hydrogen chloride as necessary (methyl orange indicator). Water (50 ml) was added, precipitating a solid. The slurry was washed with dichloromethane (3 x 30 ml), then the organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 0-7% MeOH/CH_2Cl_2). The product was triturated under diethyl ether, to afford 18 mg (6%) of the title compound as a colourless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (6H, s), 3.54 (2H, s), 3.69 (3H, s), 5.64 (2H, s), 7.48-7.61 (8H, m), 8.08 (1H, s), 8.46 (2H, m); MS (ES^+) m/e 441 [MH^+].

EXAMPLE 4

[1-Methyl-5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1*H*-1,2,4-triazol-3-yl]methanol

a) 4-Bromo-1,2-dihydropyridazine-3,6-dione

A mixture of bromomaleic anhydride (50 g, 280 mmol) and sodium acetate (76.5 g, 560 mmol) in 40% acetic acid/water (750 ml) was treated with hydrazine monohydrate (16.5 ml, 340 mmol) at room temperature under nitrogen. The brown solution was stirred and heated at 100°C for 18 hours. After cooling the mixture was poured into water (1 l) and extracted with ethyl acetate (6 x 500 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated to afford 20 g (37%) of the title compound as an orange solid: ^{1}H NMR (250 MHz, DMSO-*d*$_6$) δ 7.68 (1H, br s); MS (ES$^+$) m/e 191/193 $[MH]^+$. This material was used without further purification.

b) 4-Bromo-3,6-dichloropyridazine

A solution of 4-bromo-1,2-dihydropyridazine-3,6-dione (10 g, 52 mmol) in phosphorus oxychloride (100 ml) was stirred and heated at 100°C under nitrogen for 16 h. After cooling the excess phosphorus oxychloride was removed *in vacuo*. The residue was azeotroped with toluene (x2), then taken up in dichloromethane/water. The mixture was carefully basified with solid sodium hydrogen carbonate. It was necessary to further dilute the mixture to get two clear layers. The two layers were separated and the aqueous was extracted with dichloromethane (x3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica gel, CH_2Cl_2) to afford 5.0 g (42%) of the title compound as a colourless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68 (1H, br s); MS (ES$^+$) m/e 228/230 $[MH]^+$.

c) 3,6-Dichloro-4-(pyrrolidin-1-yl)pyridazine

To a slurry of 4-bromo-3,6-dichloropyridazine (115 g, 0.51 mol) and potassium carbonate (209 g, 1.5 mol) in DMF (1 l) was added pyrrolidine (46 ml, 0.56 mol) at 0°C with stirring. The mixture was allowed to warm to room temperature and then stirred under nitrogen overnight. Water (1.5 l) was added and the resultant slurry was filtered. The residue was washed thoroughly with water and diethyl ether, yielding the title compound (110 g, 100%) as a fine white powder: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (4H, m), 3.64 (4H, m), 6.46 (1H, s); MS (ES^+) m/e 218/220 $[MH]^+$.

d) [6-Chloro-5-(pyrrolidin-1-yl)pyridazin-3-yl]hydrazine

A solution of 3,6-dichloro-4-(pyrrolidin-1-yl)pyridazine (53 g, 0.24 mol) and hydrazine monohydrate (105 ml, 2.2 mol) in 1,4-dioxane (820 ml) was heated at reflux overnight. The solution was allowed to cool, and dichloromethane was added, precipitating a solid. This was filtered off, affording the title compound as a pale yellow solid (14 g, 27%). The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 2-5% MeOH/CH_2Cl_2 containing 0.1% concentrated aqueous ammonia) yielding a further 5 g (4%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.98 (4H, m), 3.26 (2H, br s), 3.57 (4H, m), 6.11 (1H, s), 6.41 (1H, br s); MS (ES^+) m/e 214/216 $[MH]^+$.

e) *N*-Benzylidene-*N'*-[6-chloro-5-(pyrrolidin-1-yl)pyridazin-3-yl]hydrazine

To a solution of [6-chloro-5-(pyrrolidin-1-yl)pyridazin-3-yl]hydrazine (14 g, 0.063 mol) in 0.1 N hydrochloric acid (600 ml) was added benzaldehyde (6.4 ml, 0.063 mol) dropwise at room temperature. The mixture was stirred at 60°C for 15 min, yielding a thick slurry. The pH of the solvent was adjusted to ~11 with 4 N aqueous sodium hydroxide solution, and the precipitate was filtered off. The residue was washed with water, ethanol and diethyl ether, yielding 14 g (73%) of the title

compound as a white solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.93 (4H, m), 3.58 (4H, m), 6.57 (1H, s), 7.35 (1H, m), 7.39 (2H, m), 7.66 (2H, d, *J* 7.1 Hz), 8.06 (1H, s), 11.16 (1H, s); MS (ES$^+$) m/e 302/304 [MH]$^+$.

f) 6-Chloro-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

A slurry of *N*-benzylidene-*N'*-[6-chloro-5-(pyrrolidin-1-yl)pyridazin-3-yl]hydrazine (14 g, 0.046 mol) and lead(IV) acetate (24 g, 0.055 mol) in acetic acid (300 ml) was stirred at 60°C under nitrogen overnight. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (silica gel, 0-10% MeOH/EtOAc) to give 4.1 g (30%) of the title compound as a yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05 (4H, m), 3.56 (4H, m), 7.05 (1H, s), 7.51 (3H, m), 8.42 (2H, m); MS (ES$^+$) m/e 300/302 [MH]$^+$.

g) 6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 75% yield using the procedure described in Example 1, step g, with [5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-yl]methanol being used instead of *N*-(5-hydroxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-*N,N*-dimethylamine, and with 6-chloro-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine being used instead of 6-chloro-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine. Data for the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 1.92 (4H, m), 3.39 (4H, m), 3.99 (3H, s), 4.76 (2H, s), 5.54 (2H, s), 6.60 (1H, s), 7.41-7.53 (3H, m), 8.30 (2H, m); MS (ES$^+$) m/e 521 [MH$^+$].

h) [1-Methyl-5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1*H*-1,2,4-triazol-3-yl]methanol

This was prepared in 92% yield following the procedure described in Example 2, step c, but using 6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-

triazolo[4,3-*b*]pyridazine instead of 6-[5-(*tert*-butyldimethylsilanyloxy-methyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine. Data for the title compound: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.90 (4H, m), 3.47 (4H, m), 4.40 (2H, s), 5.23 (1H, br s), 5.64 (2H, s), 6.83 (1H, s), 7.47-7.59 (3H, m), 8.31 (2H, m); MS (ES$^+$) m/e 407 [MH$^+$].

EXAMPLE 5

6-(5-Chloromethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

[1-Methyl-5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1*H*-1,2,4-triazol-3-yl]methanol (from Example 4, step h) (1.0 g, 2.5 mmol) was stirred in phosphorus oxychloride (50 ml) at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane (50 ml) and water (50 ml). The aqueous phase was washed with more dichloromethane (2 x 50 ml), then the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was eluted through a plug of silica with 7.5% methanol in dichloromethane, yielding 1.2 g (100%) of the title compound as a colourless solid. An analytically pure sample was obtained after recrystallisation from ethanol/ethyl acetate/hexane. Data for the title compound: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.96 (4H, m), 3.68 (4H, m), 3.92 (3H, s), 4.72 (2H, s), 5.73 (2H, s), 6.81 (1H, s), 7.68 (3H, m), 8.29 (2H, m); MS (ES$^+$) m/e 425/427 [MH$^+$].

EXAMPLE 6

N-[5-(3-Phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine

To dimethylamine hydrochloride (73 mg, 0.90 mmol) in

N,N-dimethylacetamide (2 ml) was added sodium hydride (60% dispersion in mineral oil; 88 mg, 2.2 mmol) and the resultant slurry was stirred at room temperature under nitrogen for 90 min. 6-(5-Chloromethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine (from Example 5) was added (99 mg, 0.23 mmol) and the mixture was stirred at 50°C under nitrogen for 18 h. Water (15 ml) was added, and the solution was washed with dichloromethane (3 x 10 ml). The combined organic layers were washed with water (1 x 10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residual oil was triturated under diethyl ether/hexane to give a solid. This was recrystallised from ethyl acetate/ethanol/hexane, yielding 13 mg (13%) of the title compound as colourless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (4H, m), 2.34 (6H, s), 3.46 (4H, m), 3.57 (2H, s), 3.93 (3H, s), 5.56 (2H, s), 6.72 (1H, s), 7.44-7.54 (3H, m), 8.33 (2H, m); MS (ES^+) m/e 434 [MH^+], 218 [MH^{2+}]/2.

EXAMPLE 7

6-[2-Methyl-5-(morpholin-4-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine hydrochloride

This was prepared in 31% yield following the procedure described in Example 6, except using morpholine instead of dimethylamine hydrochloride, and dissolving the free base in methanolic hydrogen chloride prior to recrystallisation. Data for the title compound: ^{1}H NMR (360 MHz, DMSO-*d*$_6$) δ 1.94 (4H, m), 3.63 (4H, m), 3.83 (8H, br m), 3.97 (3H, s), 4.40 (2H, s), 5.76 (2H, s), 6.83 (1H, s), 7.64 (3H, m), 8.27 (2H, m); MS (ES^+) m/e 476 [MH^+], 239 [MH^{2+}]/2.

EXAMPLE 8

6-[5-(Azetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 23% yield following the procedure described in Example 6, but using azetidine instead of dimethylamine hydrochloride. Data for the title compound: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.95 (4H, m), 2.10 (2H, quintet, *J* 7.0 Hz), 3.33 (4H, t, *J* 7.0 Hz), 3.44 (4H, m), 3.65 (2H, s), 3.93 (3H, s), 5.54 (2H, s), 6.68 (1H, s), 7.45-7.53 (3H, m), 8.30 (2H, m); MS (ES$^+$) m/e 446 [MH$^+$], 224 [MH^{2+}]/2.

EXAMPLE 9

6-[2-Methyl-5-(4-methylpiperazin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 38% yield following the procedure described in Example 6, but using 1-methylpiperazine instead of dimethylamine hydrochloride. Data for the title compound: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.95 (4H, m), 2.28 (3H, s), 2.48 (4H, br s), 2.63 (4H, br s), 3.43 (4H, m), 3.66 (2H, s), 3.95 (3H, s), 5.56 (2H, s), 6.68 (1H, s), 7.43-7.53 (3H, m), 8.33 (2H, m); MS (ES$^+$) m/e 489 [MH$^+$], 245 [MH^{2+}]/2.

EXAMPLE 10

6-[5-(3,3-Difluoroazetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxyl-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

a) 1-Benzhydrylazetidin-3-one

To 1-benzhydrylazetidin-3-ol (10 g, 0.042 mol) and triethylamine (58 ml, 42 g, 0.42 mol) in DMSO (100 ml) at 15°C was added sulfur trioxide-pyridine complex (40 g, 0.25 mol) in DMSO (50 ml) over 5 min. The reaction was stirred at room temperature under nitrogen for 3.5 h, and was then poured onto a mixture of crushed ice (200 g) and saturated ammonium chloride solution (100 ml). The slurry was extracted with ethyl acetate (3 x 200 ml), then the combined organic layers were washed

with saturated aqueous ammonium chloride (200 ml) and water (200 ml), dried ($MgSO_4$), and concentrated *in vacuo* to leave 6.4 g (64%) of the title compound as a pale yellow solid: ^1H NMR (250 MHz, $CDCl_3$) δ 4.00 (4H, s), 4.59 (1H, s), 7.18-7.34 (6H, m), 7.47 (4H, m).

b) 1-Benzhydryl-3,3-difluoroazetidine

To 1-benzhydrylazetidin-3-one (5.0 g, 0.021 mol) in benzene (50 ml) was added diethylaminosulfur trifluoride (7.8 ml, 0.063 mol), and the mixture was stirred at room temperature under nitrogen overnight. The solution was partitioned between water (100 ml) and ethyl acetate (100 ml), then the organic layer was washed with water (100 ml) and saturated sodium chloride solution (1 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 10% EtOAc/hexane) and was then recrystallised from hexane, yielding 3.0 g (54%) of the title compound as a colourless solid: ^1H NMR (250 MHz, $CDCl_3$) δ 3.51 (4H, t, *J* 12 Hz), 4.44 (1H, s), 7.16-7.32 (6H, m), 7.42 (4H, m).

c) 3,3-Difluoroazetidine hydrochloride

1-Benzhydryl-3,3-difluoroazetidine (3.0 g, 0.011 mol) was hydrogenated in a mixture of methanol (70 ml) and 2 N hydrochloric acid (7 ml) over palladium hydroxide catalyst (20% on activated carbon, 600 mg), at 50 psi for 18 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was triturated under diethyl ether, yielding 1.3 g (88%) of the title compound as a pale yellow solid: ^1H NMR (250 MHz, DMSO-*d*$_6$) δ 4.50 (2H, t, *J* 12 Hz), 10.05 (2H, br s).

d) 6-[5-(3,3-Difluoroazetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 20% yield using the procedure described in Example 6, but using 3,3-difluoroazetidine hydrochloride instead of

dimethylamine hydrochloride. Data for the title compound: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.96 (4H, m), 3.44 (4H, m), 3.75 (4H, t, *J* 12 Hz), 3.84 (2H, s), 3.95 (3H, s), 5.55 (2H, s), 6.69 (1H, s), 7.49 (3H, m), 8.30 (2H, m); MS (ES^+) m/e 463 $[M-F]^+$.

EXAMPLE 11

6-[2-Methyl-5-(pyrrolidin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine

This was prepared in 3% yield using the procedure described in Example 6, but using pyrrolidine instead of dimethylamine hydrochloride. Data for the title compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (2H, m), 1.92 (6H, m), 3.09 (2H, m), 3.40 (2H, m), 3.56 (4H, m), 3.96 (3H, s), 4.46 (2H, s), 5.74 (2H, s), 6.86 (1H, s), 7.59 (3H, m), 8.25 (2H, m); MS (ES) m/e 460 $[MH]^+$, 230 $[MH^{2+}]/2$.

EXAMPLE 12

7-*tert*-Butyl-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

a) 4-*tert*-Butyl-3,6-dichloropyridazine

Concentrated sulphuric acid (53.6 ml, 1.0 mol) was added carefully to a stirred suspension of 3,6-dichloropyridazine (50.0 g, 0.34 mol) in water (1.25 l). This mixture was then heated to 70°C (internal temperature) before the addition of trimethylacetic acid (47.5 ml, 0.41 mol). A solution of silver nitrate (11.4 g, 0.07 mol) in water (20 ml) was then added over approximately 1 min. This caused the reaction mixture to become milky in appearance. A solution of ammonium persulphate (230 g, 1.0 mol) in water (0.63 l) was then added over 20-30 min. The internal temperature rose to approximately 85°C. During the addition the product formed as a

sticky precipitate. Upon complete addition the reaction was stirred for an additional 10 min, then allowed to cool to room temperature. The mixture was then poured onto ice and basified with concentrated aqueous ammonia, with the addition of more ice as required to keep the temperature below 10°C. The aqueous was extracted with dichloromethane (3 x 300 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give 55.8 g of crude product as an oil. This was purified by flash chromatography (silica gel, 0-15% EtOAc/hexane) to give 37.31 g (53%) of the title compound: ^1H NMR (360 MHz, DMSO-d_6) δ 1.50 (9H, s), 7.48 (1H, s); MS (ES^+) m/e 205/207 $[MH]^+$.

b) 7-*tert*-Butyl-6-chloro-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

A mixture of 4-*tert*-butyl-3,6-dichloropyridazine (20 g, 0.097 mol), 2-fluorobenzhydrazide (22.6 g, 0.145 mol) and triethylamine hydrochloride (20 g, 0.0145 mol) in dioxane (1.2 l) was stirred and heated at reflux under a stream of nitrogen for 4 days. Upon cooling the volatiles were removed *in vacuo* and the residue was triturated with dichloromethane (200 ml), filtered and concentrated under vacuum. The residue was purified by chromatography (silica gel, 0-25% EtOAc/CH_2Cl_2) to give 12.95 g (44%) of the title compound as a white solid: ^1H NMR (360 MHz, $CDCl_3$) δ 1.57 (9H, s), 7.26-7.35 (2H, m), 7.53-7.60 (1H, m), 7.89-7.93 (1H, m), 8.17 (1H, s), MS (ES^+) m/e 305/307 $[MH]^+$.

c) 7-*tert*-Butyl-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

To a stirred solution of 7-*tert*-butyl-6-chloro-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (1.0087 g, 3.31 mmol) in anhydrous DMF (22 ml) under nitrogen was added [5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-yl]methanol (from Example 2, step a) (1.0224 g, 3.97 mmol) then sodium hydride (60% dispersion in oil; 0.1589 g, 3.97

mmol) portionwise over 2 min. The mixture was stirred for 30 min at room temperature. Water (78 ml) was added and the resulting solid was collected by filtration, washed with water, then hexane, and dried at 60°C under vacuum to leave 1.6129 g (93%) of the title compound as a white solid: mp 121-123°C (CH_2Cl_2-EtOAc-hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.90 (9H, s), 1.40 (9H, s), 3.79 (3H, s), 4.73 (2H, s), 5.49 (2H, s), 7.27 (1H, m), 7.33 (1H, t, *J* 7.6 Hz), 7.56 (1H, m), 7.87 (1H, td, *J* 7.4, *J'* 1.7 Hz), 7.98 (1H, s); MS (ES^+) m/e 526 $[MH]^+$. Anal. Found C, 59.31; H, 6.91; N, 18.53. $C_{26}H_{36}FN_7O_2Si$ requires C, 59.40; H, 6.90; N, 18.65%.

EXAMPLE 13

[5-(7-*tert*-Butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol

This was prepared in 93% yield using a similar procedure to that described in Example 2, step c, but using 7-*tert*-butyl-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine instead of 6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazine. Data for title compound: mp 225-230°C (CH_2Cl_2-EtOAc); ^1H NMR (360 MHz, $CDCl_3$) δ 1.41 (9H, s), 2.34 (1H, br t), 3.80 (3H, s), 4.72 (2H, d, *J* 5.6 Hz), 5.50 (2H, s), 7.28 (1H, m), 7.35 (1H, t, *J* 7.6, *J'* 1.0 Hz), 7.57 (1H, m), 7.87 (1H, td, *J* 7.4, *J'* 1.8 Hz), 7.99 (1H, s); MS (ES^+) m/e 412 $[MH]^+$. Anal. Found C, 58.14; H, 5.24; N, 23.70. $C_{20}H_{22}FN_7O_2$ requires C, 58.39; H, 5.39; N, 23.83%.

EXAMPLE 14

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(5-methoxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

To a stirred mixture of [5-(7-*tert*-butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol (from Example 13) (0.1017 g, 0.247 mmol) in anhydrous DMF (5 ml) under nitrogen was added sodium hydride (60% dispersion in oil; 10.9 mg, 0.273 mmol). The mixture was stirred at room temperature for 5 min, then iodomethane (18.5 µl, 0.297 mmol) was added dropwise. The mixture was stirred for a further 3 h, adding more sodium hydride (60% dispersion in oil; 1.1 mg, 0.028 mmol) after 45 min. Water (20 ml) was added and the mixture was filtered, washing the solid with more water. Saturated aqueous NaCl was added to the filtrate and this was extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 3% MeOH/CH_2Cl_2) to give 80.0 mg (76%) of the title compound as a white solid: mp 138-140°C (CH_2Cl_2-EtOAc-isohexane); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.40 (9H, s), 3.47 (3H, s), 3.82 (3H, s), 4.51 (2H, s), 5.50 (2H, s), 7.27 (1H, m), 7.35 (1H, t, *J* 7.5, *J'* 0.9 Hz), 7.56 (1H, m), 7.88 (1H, td, *J* 7.4, *J'* 1.8 Hz), 7.99 (1H, s); MS (ES^+) m/e 426 $[MH]^+$. Anal. Found C, 59.02; H, 5.48; N, 22.74. $C_{21}H_{24}FN_7O_2$ requires C, 59.28; H, 5.69; N, 23.05%.

EXAMPLE 15

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

a) 7-*tert*-Butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-one

To a stirred solution of 7-*tert*-butyl-6-chloro-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (from Example 12, step b) (1.0468 g, 3.43 mmol) in 1,4-dioxane (60 ml) and water (12 ml) was added 4 M aqueous NaOH (4.29 ml, 17.2 mmol), and the solution was heated at reflux for 23 h. The solvent was removed *in vacuo* and the residue was partitioned between

water (200 ml) and diethyl ether (100 ml). The aqueous layer was then acidified to pH ≤3 with 5 M aqueous HCl. The resulting precipitated solid was collected by filtration, washed with water, then hexane, and dried at 60°C under vacuum to give 0.8990 g (91%) of the title compound as a white solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.40 (9H, s), 7.40-7.48 (2H, m), 7.65 (1H, m), 7.84 (1H, td, *J* 7.3, *J'* 1.8 Hz), 8.00 (1H, s), 12.64 (1H, br s); MS (ES$^+$) m/e 287 [MH]$^+$.

b) 7-*tert*-Butyl-6-cyanomethoxy-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

To a stirred solution of 7-*tert*-butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-one (0.8953 g, 3.13 mmol) in anhydrous DMF (47 ml) under nitrogen was added sodium hydride (60% dispersion in oil, 0.1878 g, 4.70 mmol) and the mixture was stirred at room temperature for 25 min, then at 80°C for 25 min. After allowing to cool, bromoacetonitrile (0.327 ml, 4.69 mmol) was added dropwise and the mixture was stirred at room temperature for 18 h. Water (160 ml) was then added and the resulting precipitated solid was collected by filtration, washed with water, then hexane, and dried at 60°C under vacuum to afford 0.8506 g (84%) of the title compound as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (9H, s), 5.07 (2H, s), 7.30 (1H, m), 7.36 (1H, td, *J* 7.6, *J'* 0.9 Hz), 7.57 (1H, m), 7.93 (1H, td, *J* 7.3, *J'* 1.8 Hz), 8.04 (1H, s); MS (ES$^+$) m/e 326 [MH]$^+$.

c) 7-*tert*-Butyl-3-(2-fluorophenyl)-6-(5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

To a stirred solution of 7-*tert*-butyl-6-cyanomethoxy-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (0.5455 g, 1.68 mmol) in anhydrous methanol (7 ml) under nitrogen was added a 0.4 M solution of sodium methoxide in methanol (0.126 ml, 0.0504 mmol), and the mixture was stirred at room temperature for 5 h. The mixture was neutralised by adding acetic acid (2.9 µl, 0.051 mmol), then trifluoroacetic hydrazide

(Fritz, H. *et al.*, *Magn. Reson. Chem.*, 1990, *28*, 331-336) (0.2246 g, 1.75 mmol) in anhydrous methanol (2 ml) was added, and the mixture was heated at 60°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 5% $MeOH/CH_2Cl_2$) to leave 0.6893 g (94%) of the title compound as a white solid: mp 206-217°C ($CHCl_3$-EtOAc-isohexane); ^1H NMR (360 MHz, $CDCl_3$) δ 1.34 (9H, s), 5.70 (2H, s), 7.13 (1H, m), 7.22 (1H, t, *J* 7.5 Hz), 7.45 (1H, m), 7.72 (1H, m), 8.83 (1H, s); MS (ES^+) m/e 436 $[MH]^+$. Anal. Found C, 52.70; H, 3.78; N, 22.31. $C_{19}H_{17}F_4N_7O$ requires C, 52.42; H, 3.94; N, 22.52%.

EXAMPLE 16

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(2-methyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine and 7-*tert*-Butyl-3-(2-fluorophenyl)-6-(1-methyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

To a stirred mixture of sodium hydride (60% dispersion in oil; 32.7 mg, 0.818 mmol) and iodomethane (50.7 μl, 0.814 mmol) in anhydrous DMF (4 ml), cooled under nitrogen to -3°C, was added dropwise, over 11 min, a solution of 7-*tert*-butyl-3-(2-fluorophenyl)-6-(5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine (from Example 15) (0.2953 g, 0.678 mmol) in anhydrous DMF (6 ml). The mixture was stirred at -2°C for 15 min, then allowed to warm to 18°C over 2 h, and stirred at this temperature for a further 45 min. The mixture was partitioned between ethyl acetate (40 ml) and brine (40 ml). The aqueous layer was extracted further with ethyl acetate (40 ml), and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 2% $MeOH/CH_2Cl_2$) to afford 0.2405 g (79%) of a 4:1 mixture of the two title

compounds as a white solid. These were separated by flash chromatography (silica gel, 70-100% EtOAc/isohexane).

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(2-methyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine: mp 139-141°C (CH_2Cl_2-EtOAc-isohexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 4.04 (3H, s), 5.46 (2H, s), 7.25 (1H, m), 7.32 (1H, td, *J* 7.6, *J'* 0.9 Hz), 7.53 (1H, m), 7.92 (1H, td, *J* 7.5, *J'* 1.7 Hz), 7.96 (1H, s); MS (ES^+) m/e 450 $[MH]^+$. Anal. Found C, 52.94; H, 4.11; N, 21.19. $C_{20}H_{19}F_4N_7O.0.3H_2O$ requires C, 52.82; H, 4.34; N, 21.56%.

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(1-methyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine: mp 160-162°C (CH_2Cl_2-EtOAc-isohexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 3.85 (3H, s), 5.54 (2H, s), 7.25 (1H, m), 7.33 (1H, td, *J* 7.6, *J'* 1.0 Hz), 7.54 (1H, m), 7.84 (1H, td, *J* 7.4, *J'* 1.7 Hz), 7.99 (1H, s); MS (ES^+) m/e 450 $[MH]^+$. Anal. Found C, 53.43; H, 4.19; N, 21.89. $C_{20}H_{19}F_4N_7O$ requires C, 53.45; H, 4.26; N, 21.82%.

EXAMPLE 17

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(2-ethyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine and 7-*tert*-Butyl-3-(2-fluorophenyl)-6-(1-ethyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

These were prepared in an overall yield of 92% following a similar procedure to that described in Example 16, but using iodoethane instead of iodomethane.

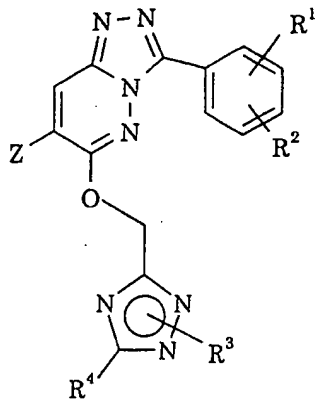
7-*tert*-Butyl-3-(2-fluorophenyl)-6-(2-ethyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine: mp 132-140°C (CH_2Cl_2-EtOAc-isohexane); ^1H NMR (360 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.49 (3H, t, *J* 7.3 Hz), 4.33 (2H, d, *J* 7.3 Hz), 5.48 (2H, s), 7.25 (1H, m), 7.32

(1H, td, *J* 7.6, *J'* 1.0 Hz), 7.53 (1H, m), 7.93 (1H, td, *J* 7.4, *J'* 1.7 Hz), 7.96 (1H, s); MS (ES^+) m/e 464 $[MH]^+$.

7-*tert*-Butyl-3-(2-fluorophenyl)-6-(1-ethyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine: mp 175-178°C (CH_2Cl_2-EtOAc-isohexane); ^1H NMR (360 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.45 (3H, t, *J* 7.3 Hz), 3.85 (2H, d, *J* 7.3 Hz), 5.56 (2H, s), 7.28 (1H, m), 7.36 (1H, td, *J* 7.5, *J'* 1.0 Hz), 7.57 (1H, m), 7.88 (1H, td, *J* 7.5, *J'* 1.8 Hz), 8.01 (1H, s); MS (ES^+) m/e 464 $[MH]^+$. Anal. Found C, 54.44; H, 4.52; N, 21.03. $C_{21}H_{21}F_4N_7O$ requires C, 54.43; H, 4.57; N, 21.16%.

CLAIMS:

1. A compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein

Z represents *tert*-butyl, cyclobutyl, phenyl or pyrrolidin-1-yl;

R^1 represents hydrogen, methyl, methoxy or fluoro;

R^2 represents hydrogen or fluoro;

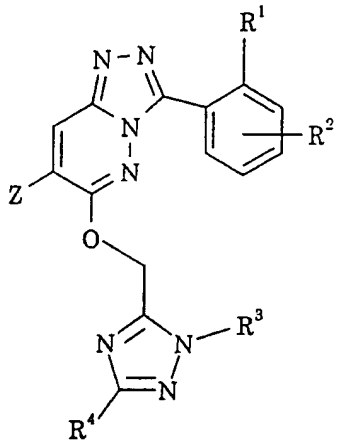
R^3 represents hydrogen, methyl or ethyl;

R^4 represents trifluoromethyl, chloromethyl, or a group of formula $-CH_2OR^a$ or $-CH_2NR^bR^c$;

R^a represents hydrogen, methyl or *tert*-butyldimethylsilanyl; and

R^b and R^c both represent methyl; or R^b and R^c together represent the residue of an azetidine, 3,3-difluoroazetidine, pyrrolidine, morpholine or *N*-methylpiperazine moiety.

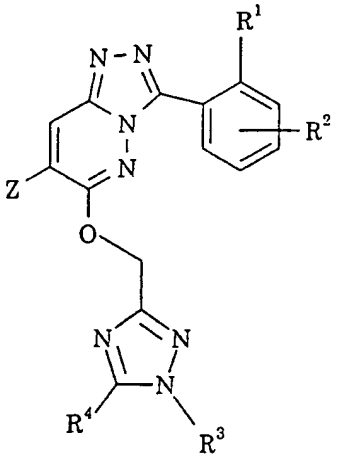
2. A compound as claimed in claim 1 represented by formula IIA, and pharmaceutically acceptable salts thereof:



(IIA)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1.

3. A compound as claimed in claim 1 represented by formula IIB, and pharmaceutically acceptable salts thereof:



(IIB)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1.

4. A compound as claimed in any one of the preceding claims wherein R^1 represents hydrogen or fluoro.

5. A compound as claimed in any one of the preceding claims wherein R^3 represents methyl or ethyl.

6. A compound selected from:

N-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol;

N-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

[1-methyl-5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1*H*-1,2,4-triazol-3-yl]methanol;

6-(5-chloromethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

N-[5-(3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-ylmethyl]-*N*,*N*-dimethylamine;

6-[2-methyl-5-(morpholin-4-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[5-(azetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[2-methyl-5-(4-methylpiperazin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[5-(3,3-difluoroazetidin-1-ylmethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

6-[2-methyl-5-(pyrrolidin-1-ylmethyl)-2*H*-1,2,4-triazol-3-ylmethoxy]-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy]-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;

[5-(7-*tert*-butyl-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yloxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl]methanol;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(5-methoxymethyl-2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(2-methyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-methyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(2-ethyl-5-trifluoromethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-ethyl-5-trifluoromethyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

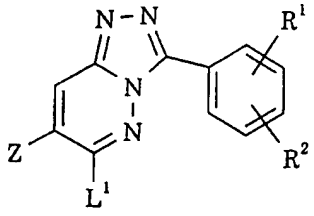
and pharmaceutically acceptable salts thereof.

7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

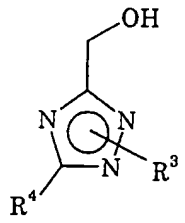
8. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of anxiety.

9. A process for the preparation of a compound as claimed in claim 1, which comprises:

(A) reacting a compound of formula III with a compound of formula IV:



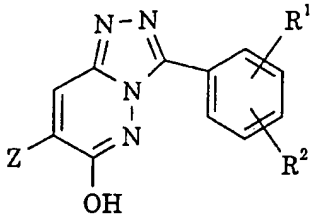
(III)



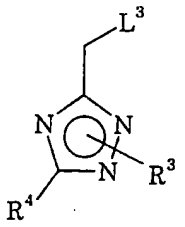
(IV)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1, and L^1 represents a suitable leaving group; or

(B) reacting a compound of formula XI (or its 1,2,4-triazolo[4,3-*b*]pyridazin-6-one tautomer) with a compound of formula XII:



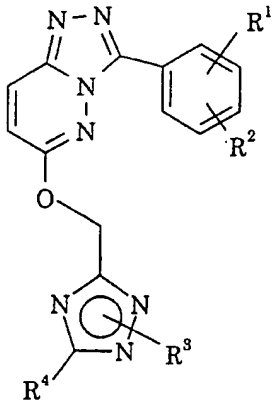
(XI)



(XII)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1, and L^3 represents a suitable leaving group; or

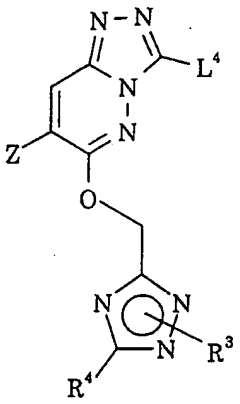
(C) reacting a compound of formula Z-CO_2H with a compound of formula XIII:



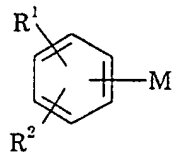
(XIII)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1; in the presence of silver nitrate and ammonium persulphate; or

(D) reacting a compound of formula XIV with a compound of formula XV:



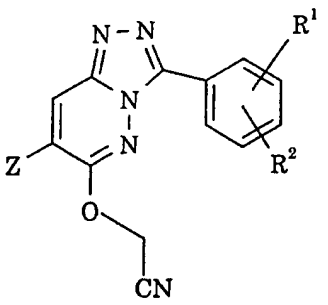
(XIV)



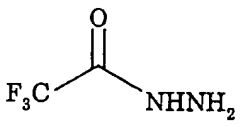
(XV)

wherein Z, R^1, R^2, R^3 and R^4 are as defined in claim 1, M represents $-B(OH)_2$ or $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst; or

(E) reacting a compound of formula XVII with the hydrazide of formula XVIII:



(XVII)



(XVIII)

wherein Z, R^1 and R^2 are as defined in claim 1; and

(F) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

10. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/00308

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/5025 A61P25/00 C07F7/18
//(C07D487/04,249:00,237:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04559 A (MERCK SHARP & DOHME (GB)) 5 February 1998 (1998-02-05) cited in the application claims 1,10	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/GB 00/00308

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